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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/876,252	06/07/2001	Dominic P. Behan	AREN-0240	8181

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/876,252	BEHAN ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *101-144* is/are pending in the application.

4a) Of the above claim(s) *133-144* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *101-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4/7/03 8/28/01
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

DETAILED ACTION

1. Amendment filed 9/24/03 has been entered.

2. Newly submitted claims 133-144 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 133-144 are directed to method of identifying candidate compounds that modulate a G protein coupled receptor comprising SEQ ID NO:30 or variants thereof. The Inventions of claims 133-144 and elected Group XXVII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the products of Group XVII can be used to make antibodies.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim133-144 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Examiner acknowledges the typographical error in paragraph 2 of the previous office Action, as pointed out by Applicant, that indicated that new claims 101-132 were drawn to the elected invention of Group XXVIII, rather than XXVII. For clarification it is noted claims 101-132 are drawn to the elected invention of Group XXVII. Further, Examiner notes that GPR38 (V297K), the elected invention of instant Application, was

referred to as GPR38 (V279K), due to typographical error, in the previous office Action. For clarification it is noted the elected invention of instant Application is GPR38 (V297K).

4. Drawing submitted by Applicant on 9/24/03 are approved by the Examiner.

Specification

5. Acknowledgment is made of applicant's claim for priority. Applicant assert that the claims of the present application should be afforded the benefit of the March 12, 1999 filing date of 60/123,945 application. Applicant's arguments have been fully considered and found persuasive. The present application is afforded the benefit of the March 12, 1999 filing date of 60/123,945 application.

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph

6. Claims 101-132 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. The rejection of claims 101-132 under 35 U.S.C. 101, dated 3/25/03 (Previous office Action), is applied to pending claims 101-132 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Applicant's arguments have been fully considered and not found persuasive. Applicant's arguments are addressed below. Applicant argues:

a) The functionality of the non-endogenous constitutively activated version of GPR38 (V297K) is shared with that of the endogenous receptor (GPR38) and the skilled

artisan would readily and immediately equate the functionalities of GPR38 with GPR38 (V297K),

b) A well established utility exists for GPR38 and, thus, for GPR38 (V297K). GPR38 (V297K) differs from GPR38 by a single amino acid and yields a constitutively active version of the endogenous receptor.

c) GPR38, which is expressed in the thyroid, has a well-established utility for the prevention of exacerbation of or treatment of Graves's disease. As indicated on pages 8 and 18 of provisional application No. 60/123,945, it was known at the time of filing that GPR38, which was disclosed as a GPCR, was expressed in the thyroid. Activation of GPR38 leads to increase in intracellular camp. Graves disease was characterized by IgG antibodies that bound to and activated the TSH receptor (a GPCR). Activation of TSH leads to an increase in intracellular cAMP. It follows that an agent that inhibits a thyroid pathway leading to an increase in intracellular camp would have a well established utility for the prevention of exacerbation of or treatment of Graves disease.

d) GPR38 (V297K) has a specific and substantial utility in that inverse antagonism of GPR38 (V297K) and by implication, GPR38, is useful in preventing or treating Graves's disease.

Applicant's arguments have been summarized above (a-d). Applicant's arguments have been fully considered but not found persuasive. Examiner is not disputing that GPR38 and GPR38 (V297K) may both be G protein coupled receptors. Based on the record, there is not a "well established utility" for the claimed invention,

GPR38 (V297K) or its related receptor GPR38. Applicant has asserted utilities for the specifically claimed invention of claims 101-132. Provisional application No. 60/123,945, pages 7, specifically states, that GPR38 is an orphan receptor, and "Gaining an understanding of the normal physiological role of [GPR38] will initially involve...identification of [its] endogenous ligand(s). Further, Provisional application No. 60/123,945, pages 7 and 8, specifically states, disclosed is that, "GPR38 has been reported to be closely related to the type 1 neurotensin receptor-1 and growth hormone secretarogue receptor of the GPCR, and is reportedly expressed in thyroid gland, stomach and bone marrow". Therefore, GPR38 is an orphan receptor for which the normal physiological role is unknown, and the endogenous ligand specific for that receptor has not been identified or is not know. As disclosed in the specification, GPCRs bind to a G protein (e.g. Gq, Gs, Gi, Gz, Go) and effect second messenger signaling which results in cellular activation or cellular inhibition. Gs stimulates the enzyme adnenylyl cyclase, Gi (Gz and Go) inhibit this enzyme. Adenylyl cyclase catalyses the conversion of ATP to cAMP. The inhibition or stimulation of adenylyl cyclase affects cAMP levels in the cell. Cyclic AMP, in turn, drives gene expression by promoting the binding of a camp-responsive DNA binding protein or transcription factor that binds to the promoter at specific sites and drives expression of specific genes. There are many genes and proteins that are directly or indirectly regulated by changes in cAMP levels. On the other hand Gq and Go are associated with activation of enzyme phospholipase C, which hydrolyses PIP2, releasing intracellular messengers DAG and IP3. It is well established in the art that although GPCRs share the same common

structural motif, they interact with specific G proteins and have divergent effects. The G protein that interacts with GPR38 is not known or disclosed. The effect of activating or inhibiting GPR38 is not known. The ligand for GPR38 is not known. The physiological function of GPR38 is not know. All GPCRs are not involves in the same disease state or dysfunction. There is no disclosure in the specification or prior art that discloses that GPR38 (V297K) or GPR38 is useful in preventing or treating Graves's disease. Although, Applicants argues Graves disease was characterized by IgG antibodies that bound to and activated the TSH receptor (a GPCR) and activation of TSH leads to an increase in intracellular cAMP it does not follow that an agent that inhibits a thyroid pathway leading to an increase in intracellular cAMP would have a well established utility for the prevention of exacerbation of or treatment of Graves disease. GPR38 or its related receptors, type 1 neurotensin receptor-1 and growth hormone secretarogue receptor, have not been disclosed to be involved in Graves disease dysfunction. There is no disclosure that changing cAMP levels in a cell by modulating GPR38 (V297K) or GPR38 would have any effect on Graves's disease. It not even known if GR38 actually increases cAMP levels upon binding ligand. The is no disclosure of what specific effect inverse antagonism of GPR38 (V297K) and by implication, GPR38, would have on Graves disease. Further, the utility of using GPR38 (V297K) to prevent or treat Grave's disease is not disclosed in the specification. The relationship of TSH receptor, GPR38, cAMP levels and Grave's disease, relied on by applicant to argue utility, were not disclosed in instant application. Therefore, using GPR38 to prevent or treat Grave's disease cannot be used to support utility in instant application.

Therefore, the specification discloses general functional activities of G-protein coupled receptors (GPCR) which may be applicable to G-protein coupled receptors but does not disclose any activity associated with the specific GPR38 (V297K), of instant invention. As disclosed in the prior Office Action, the superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant molecules, and even photons and calcium ions. The GPR38 (V297K), of instant invention is considered by the examiner to be a member of the orphan receptor of G-protein coupled receptors i.e. seven transmembrane receptor with no known endogenous ligands. Further, a position that the GPR38 (V279K), is related, through homology, to known orphan receptors may be true, but the art shows it requires more than the disclosed homology to assign a function to an orphan receptor, knowledge of the endogenous ligand for the receptor is required.

The utilities asserted by Applicant are not specific or substantial. Since no specific function of the polypeptide of instant invention is known, and the hypothesized function is based entirely on conjecture from homologous polypeptides, the asserted utilities are not specific to instant polypeptide, but rather are based on family attributes. Neither the specification nor the art of record disclose the GPR38 (V297K), fragments or variants thereof useful to identify drugs that affect said protein and modulate its activity. Similarly, neither the specification nor the art of record disclose any instances where disorders can be effected by interfering with the activity using the GPR38 (V297K), or related GPR38, or using fragments or variants thereof. Thus the

corresponding asserted utilities are essentially methods of using GPR38 (V297K), to identify disease states associated with GPR38 (V297K), dysfunction and as targets for drug discovery. Therefore the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with GPR38 (V297K), which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed GPR38 (V297K), further experimentation is necessary to attribute a utility to the claimed polypeptides and fragments thereof. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966) (noting that "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed GPR38 (V297K), further experimentation is necessary to attribute a utility to the claimed GPR38 (V297K),. The instant application does not disclose the biological role of GPR38 (V297K), or its significance. The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or

biological significance for the GPR38 (V297K), of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants claimed invention is incomplete.

Further, the rejection is based on the failure to disclose sufficient properties of the protein and/or polynucleotide to support an inference of utility. GPR38 (V279K), belongs is a family in which the members have divergent functions. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family.

The diversity of the biochemical function and the wide range of regulatory pathways involving GTP-binding proteins is well known in the art. Without some common biological activity for the family members, a new member would not have a specific, substantial, or credible utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different

biological activities which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for toxicology testing, diagnosis is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use. Further, the specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. If the expression of the claimed GPR38 (V297K), increases, is this a positive or negative outcome? Would this be a toxic response or not? The disclosure is insufficient to evaluate the results of the test in any meaningful manner.

Without knowing a biological significance of the claimed polypeptides, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a "real world" manner based on the diversity of biological activities

possessed by GTP-binding proteins. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The implication that the claimed invention has utility in testing, drug development and disease diagnosis/treatment, do not meet the standards for a specific, substantial, and or well-established utility for reasons set forth above.

In all cases a practical utility of an invention may be derived from belonging to a broad class of inventions. The requirement in any particular case, however, is that practical utility can be inferred if each and every member of the broad class possesses a common utility. The question in the instant application is whether the members of the family of proteins to which the claimed invention is structurally related have, individually, a specific, substantial and credible or well-established utility. Applicant has failed to show by a preponderance of the evidence, in enough detail, with respect to the described GPR38 (V297K), has any substantial use. The record shows that the GTP-binding protein family is diverse, and has such a broad definition, that a "common utility" cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful.

In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

7. Claims 101-132 remain rejected under 35 U.S.C. 112, first paragraph, for reasons set forth in the previous Office Action. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed cDNA encoding GPR38 (V297K), further experimentation is necessary to attribute a utility to the claimed polynucleotide.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 703-308-9435. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Nirmal S. Basi
Art Unit 1646
12/13/03

MICHAEL PAK
PRIMARY EXAMINER